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Tandem Staudinger–Aza-Wittig Templated Reaction: De Novo Synthesis of Sugar–Ureido Cryptands

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Keywords: Cryptands / Template synthesis / Carbohydrates / Crown compounds

A templated Staudinger–aza-Wittig tandem reaction selectively affords in one step a monocellobiosyl[bis(ureido)]diazacrown cryptand and a bis(cellobiosyl)tetraureido[bis(diazacrown)] cryptand. Formation of each type of cryptand was under control by Na^+ or Cs^+ template effect.

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Introduction

Crown ethers and azacrown ethers are, on the one hand, important molecular receptors that are currently used in biological model systems.[1] On the other hand, sugars are well known as versatile chiral entities that are particularly suitable for the design of chiral receptors. Crown ethers containing various carbohydrate moieties have received much attention in recent years.[2] Usually, the sugar moieties are mono-, di- or trisaccharides,[3a,3b] directly incorporated into the crown macrocycle itself or grafted as pendant arms.[3c,3d] However, the number of papers related to the synthesis of cryptands containing carbohydrate moieties and azacrown ethers in their structures is limited.[4a,4b]

We wish to report an efficient one-step sequence for access to a new type of cryptand structure incorporating bifunctionalised disaccharidyl arms as illustrated in Figure 1. Very recently, we realised a de novo synthesis of a bis-β-cyclodextrin pseudocryptand[3d] by straightforward coupling of a *C*-chiral diazacrown ether on monoazido peracetylated β-cyclodextrin by using a tandem Staudinger–aza-Wittig (SAW) reaction, also known as the "phosphane imide" reaction.[5] In this communication, we report results obtained by a one-pot, template-directed macrobicyclisation between 1,6-diazidocellobiose and a diazacrown ether macrocycle by using the tandem SAW reaction.

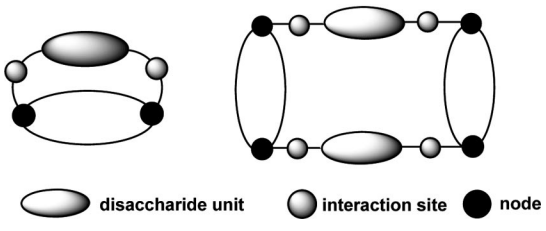

Figure 1. Conceptual design of expected cryptand structures.

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Results and Discussion

Cryptates **4** to **6** were synthesised in one pot and in fairly good yields (40–47%) from 2,2′,3,3′,4′,6-hexa-*O*-acetyl-1,6′-diazido-1,6′-dideoxy-β-D-cellobiose (**2**) or 1,6′-diazido-1,6′-dideoxy-β-D-cellobiose (**3**) and tetraoxadiazacyclooctadecane **1** by the tandem SAW reaction in anhydrous DMF by using the alkali cation template effect. Thus, from **2** and **3**, respectively, in the presence of Na_2CO_3 monocellobiosylsodium cryptates **4** and **5** were obtained. Differently, the same reaction from **2** or **3** in the presence of Cs_2CO_3 led only to bis(cellobiosyl)cesium cryptate **6** or 7 as shown in Scheme 1. The reaction performed without the cation template effect afforded, as expected, a mixture of the two cryptates (Scheme 1). Analysis of new compounds **2** to **7** by IR and NMR spectroscopy, MS (ESI) and elemental analysis revealed data that are in accordance with the proposed structures. The IR spectra of **2** and **3** show the presence of strong absorption bands at 2148 and 2118 cm^{-1}, respectively, which are characteristic of the presence of azido groups. Concerning the cryptates, the IR spectra of acetylated cryptates **4** and **6** show single absorption bands at 1648 and 1655 cm^{-1} characteristic of the urea carbonyl bonds, also confirmed by the quaternary carbon ^{13}C NMR signals at δ = 158.6 and 157.8 ppm for **4** and two signals at δ = 156.6 and 160.0 ppm for **6**. It is interesting to note that deacetylated cryptates **5** and **7** show two absorption bands at 1701, 1637 and 1699, 1635 cm^{-1}, respectively, and allow distinction between the anomeric urea carbonyl bond and 6′-urea carbonyl bond. This feature was confirmed by the

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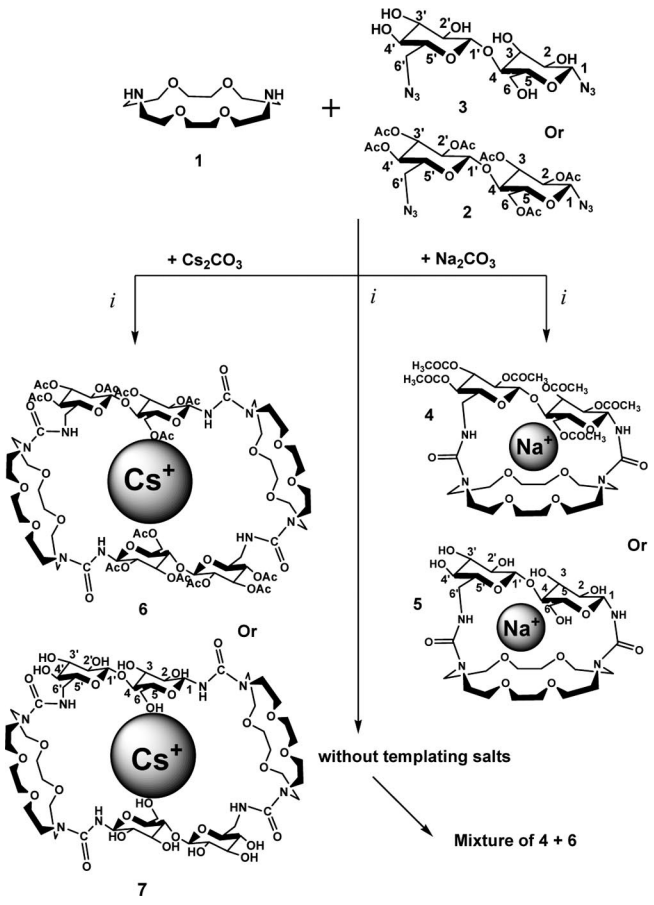
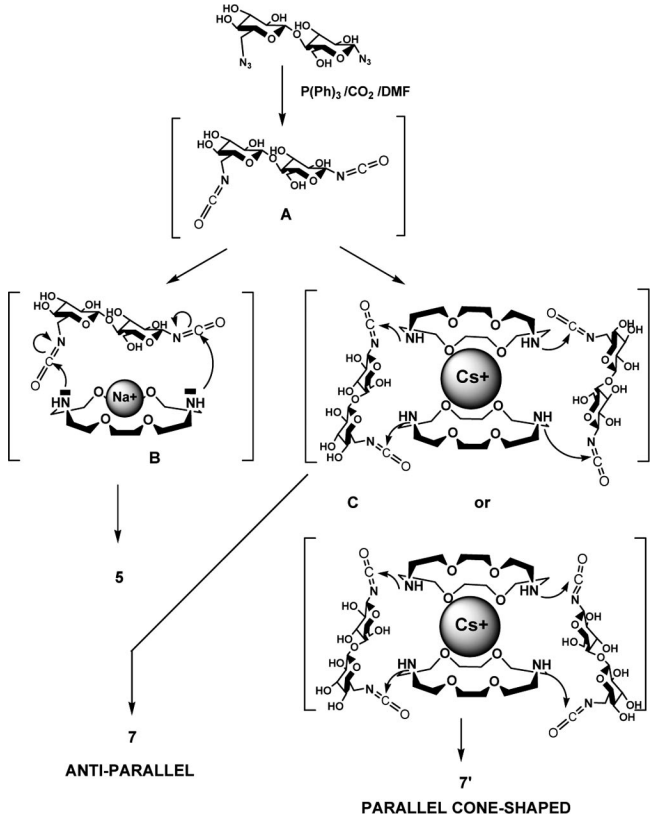
quaternary carbon ^{13}C NMR signals at 161.0, 156.3 ppm for **5** and 157.7, 157.4, 152.6 ppm for **7**. However, these results prove that coupling between the disaccharide and the diazacrown was effective and that a conformational equilibrium operates in the most flexible cryptates **6** and **7**.



Scheme 1. *i* = $P(Ph)_3/CO_2$/DMF.

Furthermore, positive ESI high-resolution mass spectra of **4** to **7** were recorded and show the presence of monocharged species $[M + Na]^+$ at *m*/*z* = 929.3464 for compound **4** and $[M + Na]^+$ and $[M + H]^+$ at *m*/*z* = 677.2 and 655.2, respectively, for the corresponding deacetylated compound **5**. The mass spectrum of **6** is more complex, as it also shows tricharged and dicharged species $[M+ Na + 2Cs]^{3+}$ at *m*/*z* = 2100.9 and $[M + 2Cs]^{2+}$ at *m*/*z* = 2077.8 and monocharged species $[M + Cs]^+$ at *m*/*z* = 1945.8, $[M + Na]^+$ at *m*/*z* = 1835.7 and $[M + H]^+$ at *m*/*z* = 1813.7. These data strengthen the proposed structures for compounds **4** to **7**. Considering the reaction pathway (Scheme 2) and the mechanism of the SAW tandem reaction (with CO_2 as the electrophile),[6a–6c] 1,6-diazidocellobiose first affords 1,6-diisocyanatocellobiose intermediate A (as predicted by the mechanism of the SAW reaction),[6a–6c] and then two nucleophilic additions take place simultaneously on the diisocyanate by the preorganised sodium B or cesium C diazacoronates, which are in the proper conformation so as to favour macrocyclisation to the final cryptates. Considering the synthesis of **6** and **7**, it should be noted that the cyclisation reaction can produce two different macrocycles: one with the two disaccharides in a parallel direction (i.e., **7′**) (Scheme 2) and the other one with the two disaccharides in an antiparallel direction (i.e., **6** and **7**). Unfortunately, at this point, the lack of X-ray structural data does not allow us to conclude definitively. Anyway, it could be suggested, on the basis of the best geometry adopted around a templating sphere, that the antiparallel arrangement is closer to a spherical spatial organisation and should be preferred over the parallel arrangement, which is more like a cone-shaped spatial organisation.



Scheme 2. Proposed reaction pathway for the templated SAW tandem reaction. C may lead to antiparallel **7** or parallel cone-shaped **7′** macrocycle.

Conclusions

In conclusion, an efficient, selective and rapid method for the preparation of a new family of macrobicyclic and macrotricyclic molecular receptors has been presented. It was demonstrated that high selectivity occurs in the reaction in the presence of sodium or cesium alkali cations and confirms that the macrocyclisation step was under the control of cations size. Presently, attempts to crystallise these compounds are being pursued. Nevertheless, we have now started a step-by-step selective synthesis of the parallel cone-shaped macrocycle that will be achieved in the near future. Finally, the synthesis of new compounds incorporating other disaccharidyl moieties and the study of their overall complexation properties are in progress.

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Experimental Section

General: All new compounds gave satisfactory spectroscopic data. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DRX-400 spectrometer, and all FTIR spectra were obtained with a Bruker Vector22 spectrometer. HRMS (ESI) spectra in the positive ion mode were obtained with a Bruker microTOF-Q98. Elemental analyses were determined with a Thermofinnigan Flash EA1112 analyzer. In all experiments DMF was dried with $CaSO_4$, filtered off, distilled from CaH_2 and flushed with argon to eliminate dimethylamine. Other reagents was purchased from Sigma–Aldrich and used as received.

2,2′,3,3′,4′,6-Hexa-*O*-acetyl-1,6′-diazido-1,6′-dideoxy-β-D-cellobiose (2): Sodium azide (0.276 g, 4.30 mmol) was added to a solution of 2,2′,3,3′,4′,6-hexa-*O*-acetyl-6′-*O*-tosyl-1-azido-β-D-cellobiose[7] (0.329 g, 0.43 mmol) in DMF (10mL). The mixture was stirred at 80 °C for 24 h. After cooling, ethyl acetate (50 mL) was added, and the mixture was washed with distilled water (2 × 50 mL). The organic phase was dried with anhydrous sodium sulfate, and then purified by column chromatography (silica gel; AcOEt/hexane, 60:40) to afford **2** (0.255 g, 92%). R_F = 0.50 (AcOEt/hexane, 60:40). IR (thin film): $\tilde{\nu}$ = 2148, 1754, 1217, 1045 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.21 (t, $J_{3',2'}$ = 9.3 Hz, $J_{3',4'}$ = 9.6 Hz, 1 H, 3′-H), 5.16 (t, $J_{3,2}$ = 9.3 Hz, $J_{3,4}$ = 9.6 Hz, 1 H, 3-H), 4.98 (t, $J_{4',3'}$ = 9.6 Hz, $J_{4',5'}$ = 9.6 Hz, 1 H, 4′-H), 4.90 (t, $J_{2',3'}$ = 9.3 Hz, $J_{2',1'}$ = 8.0 Hz, 1 H, 2′-H), 4.87 (t, $J_{2,3}$ = 9.3 Hz, $J_{2,1}$ = 8.8 Hz, 1 H, 2-H), 4.73 (d, $J_{1,2}$ = 8.8 Hz, 1 H, 1-H), 4.57 (d, $J_{1',2'}$ = 8.0 Hz, 1 H, 1′-H), 4.55 (dd, $J_{6a,6b}$ = 12 Hz, $J_{6a,5}$ = 1.8 Hz, 1 H, 6a-H), 4.13 (dd, $J_{6b,6a}$ = 12 Hz, $J_{6b,5}$ = 4.8 Hz, 1 H, 6b-H), 3.86 (t, $J_{4,3}$ = 9.6 Hz, $J_{4,5}$ = 9.3 Hz, 1 H, 4-H), 3.70 (ddd, $J_{5,4}$ = 9.3 Hz, $J_{5,6a}$ = 1.8 Hz, $J_{5,6b}$ = 4.8 Hz, 1 H, 5-H), 3.63–3.58 (m, 1 H, 5′-H), 3.44–3.35 (m, 2 H, 6′-H), 2.15, 2.09, 2.07, 2.06, 2.04, 2.00 (6 s, 18 H, 6 CH_3, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.7, 170.6, 170.1, 169.8, 169.7, 169.4 (6 *C*=O, Ac), 100.6 (C-1′), 88.2 (C-1), 75.7 (C-4), 75.23 (C-5), 73.25 (C-5′), 73.0 (C-3), 72.6 (C-3′), 72.0 (C-2), 71.4 (C-2′), 69.2 (C-4′), 62.0 (C-6), 51.3 (C-6′), 21.2–20.9 (6 CH_3, Ac) ppm. $C_{24}H_{32}N_6O_{15}$ (644.19): calcd. C 44.72, H 5.00, N 13.04; found C 44.83, H 4.91, N 12.80.

1,6′-Diazido-1,6′-dideoxy-β-D-cellobiose (3): Compound **2** (0.255 g, 0.39 mmol) was added to a solution of MeONa/methanol (100 mL) and stirred 3 h at room temperature. The mixture was then filtered through a short column of Amberlite IRN 77 resin. The filtrate was evaporated, and the resulting product was obtained as a white powder (0.145 g, 95%) and used without purification. IR (KBr): $\tilde{\nu}$ = 3416, 2117 cm^{-1}. ^{1}H NMR (200 MHz, D_2O, 25 °C): δ = 4.70 (d, $J_{1,2}$ = 8.8 Hz, 1 H, 1-H), 4.46 (d, $J_{1,2'}$ = 7.6 Hz, 1 H, 1′-H), 3.93 (d, $J_{6'a6'b}$ = 12.6 Hz,1 H, 6′a-H), 3.79–3.21 (m, 11 H, 6′b-H, 6a-H, 6b-H, 5-H, 5′-H, 4-H, 4′-H, 3-H, 3′-H, 2-H, 2′-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 104.5 (C-1′), 92.0 (C-1), 79.9 (C-4), 78.7, 77.2 (C-5, C-5′), 76.2, 76.1 (C-3, C-3′), 75.1, 74.6 (C-2, C-2′), 72.1 (C-4′), 61.8 (C-6), 52.8 (C-6′) ppm. $C_{12}H_{20}N_6O_9{\cdot}0.5H_2O$ (401.32): calcd. C 35.88, H 5.23, N 20.93; found C 36.05, H 5.18, N 20.01.

General Procedure for the Synthesis of Glycocryptands: To a flask (0.2 mmol) containing diazidocellobiose **2** or **3** was added a solution of triphenylphosphane (1.2 mmol) in anhydrous DMF (5 mL), and the mixture was stirred for 1 h at room temperature. In a second flask, the diazacrown ether (0.2 mmol) and solid Na_2CO_3 or Cs_2CO_3 (0.1 g) in anhydrous DMF (5 mL) were mixed, and the mixture was stirred for 30 min. The two mixtures were combined, and the resulting solution was stirred for 24 h at room temperature under anhydrous CO_2 bubbling. The final product was precipitated by the addition of cyclohexane or ether, filtered and washed three times with the same solvents. The pure product was dried in vacuo.

Sodium Cryptate 4: According to the general procedure, addition of **2** (0.2 mmol, 0.129 g) to **1** (0.2 mmol, 0.052 g) in the presence of Na_2CO_3 afforded **4** (0.087 g, 47%) as a pure white powder. R_F = 0.62 (AcOEt/methanol, 3:2). IR (KBr): $\tilde{\nu}$ = 3337, 2921, 1753, 1648, 1238, 1045 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C):δ = 6.68 (d, J = 9.8 Hz, 1 H, NH), 6.57 (d, J = 5.6 Hz, 1 H, NH), 5.91 (br. s, 1 H, NH), 5.79 (br. s, 1 H, NH), 5.19 (br. t, J = 9.3, 9.8 Hz, 2 H, 3′-H_{AB}), 5.15 (br. t, J = 9.8, 9.3 Hz, 2 H, 3-H_{AB}), 5.06 (br. t, J = 9.6, 9.8 Hz, 2 H, 4′-H_{AB}), 4.99–4.86 (m, 4 H, 2′-H_{AB}, 2-H_{AB}), 4.54 (br. d, J = 10.0 Hz, 2 H, 1-H_{AB}), 4.49 (br. d, J = 8.6 Hz, 2 H, 1′-H), 4.47 (br. d, J = 12.0 Hz, 2 H, 6a-H_{AB}), 4.14–406 (m, 2 H, 6b-H_{AB}), 3.97 (t large, J = 9.6, 9.8 Hz, 1 H, 4-H_A), 3.95 (br. t, J = 9.6 Hz, 1 H, 4-H_B), 3.85–2.90 (m, 56 H, 5-H_{AB}, 5′-H_{AB}, 6′-H_{AB}, 24 H, CH_2, crown ether), 2.11–1.99 (s, 36 H, CH_3, acetates) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.8–169.5 (m, *C*=O, acetates), 158.6, 157.8 (*C*=O, ureas), 100.7, 100.3 (C-1′$_{AB}$), 80.9, 80.7 (C-1$_{AB}$), 75.9, 75.8, 75.2, 74.8, 74.7, 74.6, 74.3, 74.1, 73.9, 73.3, 72.3 (C-4$_{AB}$, C-5$_{AB}$, C-5′$_{AB}$, C-3$_{AB}$, C-3′$_{AB}$, C-2$_{AB}$, C-2′$_{AB}$), 70.3 (C-4′$_{AB}$), 62.9, 62.5 (C-6,6′$_{AB}$), 50.8–42.2 (*C*H$_2$ crown ether), 21.4–20.9 (*C*H$_{3AB}$, acetates) ppm. HRMS (ES): calcd. for $C_{38}H_{58}N_4NaO_{21}$ [M + Na]$^+$ 929.3486; found 929.3464.

Sodium Cryptate 5: According to the general procedure, addition of **3** (0.2 mmol, 0.078 g) to **1** (0.2 mmol, 0.052 g) in the presence of Na_2CO_3 afforded **5** (0.062 g, 46%) as a pure white powder. IR (KBr): $\tilde{\nu}$ = 3383, 2912, 1701, 1637, 1238, 1102 cm^{-1}. ^{1}H NMR (400 MHz, CH_3OD): δ = 4.70–4.66 (m, 2 H, NH), 4.51 (d, J = 7.8 Hz, 1 H, 1′-H), 3.81–3.75 (m, 2 H), 3.68–3.21 (m, 24 H), 3.21 (s large, 6 H, OH), 3.15 (t, J = 10.0, 10.3 Hz, 1 H), 2.72 (br. s, 8 H, CH_2, crown ether) ppm. ^{13}C NMR (100 MHz, CH_3OD): δ = 161.0 (*C*=O), 156.3 (*C*=O), 105.1 (C-1′), 83.8 (C-1), 80.6, 80.1, 78.2, 77.6, 75.3, 74.8, 74.2, 66.2 (C-2,2′, C-3,3′, C-4,4′, C-5,5′), 62.2, 61.9 (C6,6′), 50.7–44.4 (*C*H$_2$ crown ether) ppm. MS (ES): *m*/*z* = 677.2 [M + Na$^+$], 655.2 [M + H]$^+$. $C_{26}H_{46}ClN_4NaO_{15}$ (713.11): calcd. C 43.79, H 6.50, N 7.86; found C 43.37, H 6.46, N 7.54.

Cesium Cryptate 6: According to the general procedure, addition of **2** (0.2 mmol, 0.129 g) to **1** (0.2 mmol, 0.052 g) in the presence of Cs_2CO_3 afforded **6** (0.171 g, 40%) as a pure white powder. IR (KBr): $\tilde{\nu}$ = 3406, 2872, 1753, 1655, 1234, 1041 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.32–4.81 (m, 5 H, 3-H, 3′-H, 4′-H, 2′-H, 2-H), 4.55–4.40 (m, 3 H, 1-H, 1′-H), 3.83–3.41 (m, 30 H, CH_2 crown ether, 6b-H, 6′-H, 5-H, 5′-H, 4-H), 2.14–1.94 (s, 18 H, CH_3, acetates) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.8–169.7 (*C*=O, acetates), 156.6, 160.0 (*C*=O, ureas), 101.3 (C-1), 80.5 (C-1′), 75.4, 74.5, 74, 73.7, 73.5, 73.0, 72.0, 68.0 (C-4, C-5, C-5′, C-3, C-3′, C-2, C-2′, C-4′), 62.9, 62.8 (C-6,6′), 51.1–41.1 (*C*H$_2$ crown ether), 21.5–20.6, (*C*H$_3$, acetates) ppm. MS (ES): *m*/*z* = 2100.9 [M + Na + 2Cs]$^{3+}$, 2077.8 [M + 2Cs]$^{2+}$, 1968.3 [M + Na + Cs]$^{2+}$, 1945.8 [M + Cs]$^+$, 1835.7 [M + Na]$^+$, 1813.7 [M + H]$^+$. HRMS (ES): calcd. for $C_{76}H_{116}N_8NaO_{42}$ [M + Na]$^+$ 1835.7079; found 1835.7085.

Cesium Cryptate 7: According to the general procedure, addition of **3** (0.2 mmol, 0.078 g) to **1** (0.2 mmol, 0.052 g) in the presence of Cs_2CO_3 afforded **7** (0.074 g, 22.6%) as a pure white powder. IR (KBr): $\tilde{\nu}$ = 3384, 2916, 1699, 1635, 1101 cm^{-1}. ^{1}H NMR (400 MHz, CH_3OD): δ = 4.64–4.66 (m, 2 H, NH), 4.63 (d, J = 8.8 Hz, 1 H, 1-H), 4.56 (d, J = 7.8 Hz, 1 H, 1′-H), 3.76–3.64 (m, 2 H), 3.68–3.21 (m, 40 H) ppm. ^{13}C NMR (100 MHz, CH_3OD): δ = 157.7, 157.4, 152.6 (*C*=O), 107.4 (C-1′), 84.7 (C-1), 79.5, 77.8, 77.6, 75.6, 74.8, 74.0, 73.8, 69.9 (C-2,2′, C-3,3′, C-4,4′, C-5,5′), 64.6, 63.3 (C-

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6,6′), 50.7–44.4 (CH_2 crown ether) ppm. MS (ES): *m*/*z* = 1441.5 $[M + Cs]^+$.

Supporting Information (see footnote on the first page of this article): Synthesis and spectroscopic data for the precursors of **2**.

Acknowledgments

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[5] This reaction presently named the "tandem Staudinger–aza-Wittig" reaction was early developed in collaboration with Hungarian colleagues in the sugar and cyclodextrin series from monoazidosaccharides and azidocyclodextrins and was initially named the "phosphane imide" reaction with respect to the first key reaction intermediate of the Staudinger reaction. See ref.[3d,6a–6c]

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[7] This product was synthesised by a known literature procedure; see compound **15** and ref. 2 in the Supporting Information.

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